

Long-Term Outcomes After Reversible Cerebral Vasoconstriction Syndrome

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Background and Purpose—We aimed to further investigate the long-term outcomes after reversible cerebral vasoconstriction syndrome (RCVS).

Methods—A longitudinal follow-up study was conducted in 173 RCVS patients.

Results—Of the 172 patients who completed a mean follow-up of 9.2 ± 3.3 years, 10 had a recurrent RCVS that was benign in all. Independent predictors of relapse were having a history of migraine and having exercise as a trigger for thunderclap headache during initial RCVS. After new delivery, the rate of postpartum RCVS was 9%.

Conclusions—Overall, long-term outcome after RCVS is excellent. (*Stroke*. 2020;51:670-673. DOI: 10.1161/STROKEAHA.119.027703.)

Key Words: cerebral arteries ■ headache ■ pregnancy ■ recurrence ■ vasoconstriction

Reversible cerebral vasoconstriction syndrome (RCVS) associates acute headache and constriction of cerebral arteries, which resolves spontaneously within 3 months.¹ Two follow-up studies have shown low relapse rates.^{2,3} Recurrence rate related to new pregnancy and delivery is unknown. To further investigate long-term outcomes after RCVS, we conducted a follow-up study in a large French prospective cohort.

Methods

Data Availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Patients

We prospectively included 173 patients from the Lariboisière Hospital cohort, which recruited all consecutive RCVS patients from 2004 to 2011.⁴ Inclusion criteria, medical history, clinical, radiological, and biological data, treatment, and assessment of reversibility of vasoconstriction have been previously described.^{4,5} Primary headaches were diagnosed according to the International Classification of Headache Disorders.⁶ Thunderclap headache was defined as a headache reaching a maximum intensity above 7/10 on an 11-point scale from 0 to 10, in <1 minute.

Follow-Up

Clinical visits were performed 3, 6, 12, and 18 months after disease onset, then every year up to 2013. Four systematic assessments were conducted in 2007, 2012, 2015, and 2017 to 2018, by phone, postal questionnaires, or emails. Events recorded included any unusual

headache, focal deficit or seizure, associated disorder, and concomitant treatments. Functional status was evaluated using the modified Rankin Scale. Recurrent RCVS was defined by the same criteria as the first bout.⁴ Patients were repeatedly instructed to consult in case of new unusual headache and to avoid vasoactive substances.

Patients who had completed at least 1 follow-up visit 6 months after the first RCVS were qualified as respondents and included in the present study.

Ethics

Ethics approval was obtained from a national French institutional review board, and written informed consent was obtained from all included patients. The database was approved by the Commission Nationale Informatique et Liberté.

Statistics

Descriptive statistics were reported. Quantitative variables are expressed by their mean \pm SD and median (and interquartile range) and qualitative variables by their number and frequency (%).

Cox models were used to analyze the impact of the variables of interest on the recurrence of RCVS, taking into account the delay between inclusion and recurrence. The proportional hazard assumption was verified. Variables with *P* values under 0.15 in the univariate Cox regression analysis were selected for a multivariate Cox model. Variables with a *P* value under 0.05 in the multivariate model after a stepwise selection of variables were considered statistically significant. Hazard ratios and 95% CIs were reported.

The event-free probabilities over time of recurrent RCVS and recurrent thunderclap headache after the first RCVS were analyzed by computing Kaplan-Meier survival curves. Incidence rates for each parameter were also calculated.

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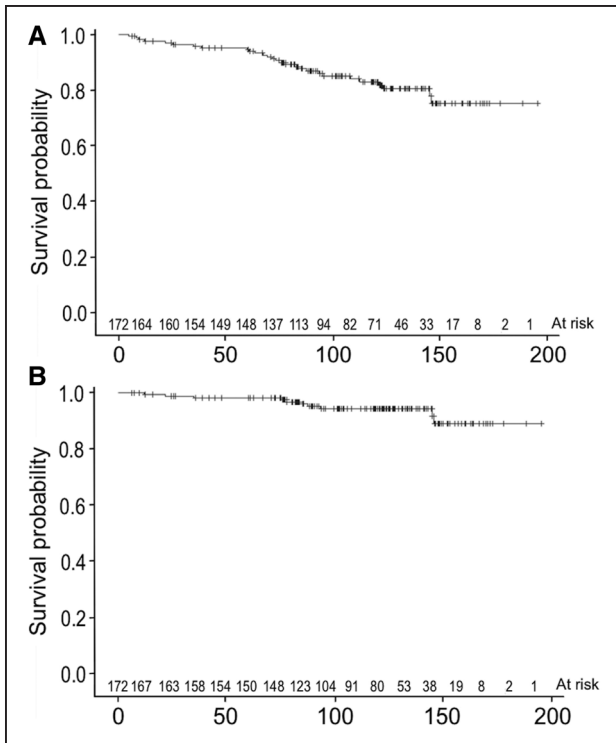


Figure 1. Survival curves. **A**, Recurrent thunderclap headache. **B**, Recurrent reversible cerebral vasoconstriction syndrome.

Statistical analyses were performed using SAS 9.1 software (SAS Institute, France) and R 3.1.1 (The R Foundation for Statistical Computing), and the statistical bilateral significance threshold was set at 5%.

Results

Recurrent RCVS

One patient was lost to follow-up before 6 months, leaving 172 respondents for the final analysis, with a mean follow-up of 110 ± 40 months (median, 118; range, 6–196; cumulative duration, 9.14 person-years). Of the 28 respondents who had new thunderclap headache (1.9 per 100 person-years [95% CI, 1.28–2.70]), 12 did not consult. Sixteen had investigations showing arterial irregularities in 10 and normal arteries in 6. Final diagnoses included primary thunderclap headache (9), primary headache associated with sexual activity (4), primary exercise headache (2), primary cough headache (2, with pansinusitis in 1), airplane headache (1), and RCVS (10 cases, all females; Figure 1).

Recurrent RCVS (0.65 per 100 person-years [95% CI, 0.329–1.154]) occurred a mean of 78 ± 46 months (median 82, range, 12–143.5) after the first episode. One patient had a third bout. Initial RCVS was secondary in 4 patients (vasoconstrictors 4, with recent infection 1). Relapse was secondary in 4 patients (vasoconstrictors 3, postpartum 1).

All 10 patients with recurrent RCVS had thunderclap headache during both bouts, 5 patients had blood pressure surge during the first bout, and 4 during relapse. None had a focal deficit or a seizure during both RCVS. During initial RCVS, 4 patients had a cortical subarachnoid hemorrhage, of whom 2 also developed a complication during relapse (asymptomatic

small infarction with hemorrhagic transformation in 1, small cortical subarachnoid hemorrhage in 1). At 3 months, all 10 patients had a modified Rankin Scale =0 during both bouts.

One patient had a stroke during recurrent RCVS (0.065 per 100 person-years [95% CI, 0.033–0.115]), but without focal deficit. By the end of the study, 2 patients had died, including 1 from a cardiovascular death at age 46 years.

The Table compares features in patients with and without recurrent RCVS, after exclusion of the deceased patient, and presents results of the univariate Cox regression analysis. Furthermore, according to Cox multivariate analysis, independent predictors of recurrent RCVS were having a history of migraine (hazard ratio, 4.5 [95% CI, 1.2–17.3] and $P=0.0260$) and having exercise as a trigger for the first or for any thunderclap headache during initial RCVS (hazard ratio, 8.4 [95% CI, 2.2–31.31] and $P=0.0016$ and hazard ratio, 4.6 [95% CI, 1.3–15.9] and $P=0.0170$, respectively).

Pregnancy and Delivery After RCVS

Sixty women were nonmenopausal at inclusion (mean age 39 ± 7 years; Figure 2). Of the 14 women with postpartum RCVS, 5 had 6 new pregnancies, 2 delivered a healthy child without recurrent RCVS, and the 3 others underwent 4 induced abortions, including 2 women who could not cope with the fear of a recurrence. Of the 46 women with initial RCVS unrelated to postpartum, 6 had 10 new pregnancies. One underwent induced abortion; 1 had 3 pregnancies, 2 had 2 pregnancies, and 2 had 1 pregnancy. They delivered 9 healthy children. Given that 1 of the 11 deliveries was followed by RCVS, the incidence rate of postpartum RCVS after a new delivery was 9%.

Discussion

In line with the Taiwanese and American follow-up studies, our results confirm that the long-term recurrence rate of RCVS is low and that relapse is mostly benign.^{2,3} In addition, our study suggests that a new pregnancy after RCVS does not carry a high risk.

The recurrence rate of RCVS in our study was 2.6-fold lower than in the Taiwanese cohort (0.65 versus 1.71 per 100 person-years).² The rate could have been underestimated in our study because not all patients with new thunderclap headache had investigations. Given that 16% of our patients had new thunderclap headache, the maximal estimated incidence rate for recurrent RCVS (definite or supposed) would be 1.9 per 100 person-years, which is still low. Because the initial RCVS was secondary to vasoactive substances in 43% of our French patients as compared to only 1.5% of the Taiwanese cohort,⁷ advices to avoid vasoconstrictors could have decreased the recurrence rate in our cohort.

In the Taiwanese study, having sexually triggered thunderclap headache during initial RCVS was the only risk factor of recurrence.² In our study, variables predicting recurrence were having exercise-triggered thunderclap headache during RCVS and having a history of migraine. Migraine, a known risk factor for hemorrhagic RCVS,⁸ is also suspected to be a risk factor for RCVS, although this latter hypothesis would require confirmation by a case-control study.¹

Table. Recurrent RCVS: Demographic Characteristics, Risk Factors, Clinical and Radiological Features, and Outcome

Variables Assessed at Initial RCVS	Recurrent RCVS; n=10	No Recurrent RCVS and no CVD; n=161	Univariate Cox Regression Analysis P Value
Age, mean±SD	46±10	44±12	0.64
Sex, female	10	112	...
History of hypertension	2	24	0.58
Migraine	6	49	0.04
Thunderclap headache previous to RCVS	2	15	0.20
History of anxiety/depression	2	47	0.54
Secondary cause for initial RCVS	5	100	0.40
Any vasoactive substance	4	79	0.51
Postpartum (% in women)	0	14	...
Any physical trigger for first headache	7	87	0.29
Sexual activity	2	33	0.95
Cough and other Valsalva maneuvers	1	21	0.74
Exertion	4	16	0.003
Any emotional precipitant	3	49	0.99
Headache during RCVS	10	161	
Thunderclap headache at onset	9	131	0.49
Recurrent headache attacks	10	144	...
Sexual trigger for ≥1 headache(s)	3	42	0.68
Emotion as trigger for ≥1 headache(s)	3	29	0.43
Exertion as trigger for ≥1 headache(s)	5	33	0.02
Any focal neurological deficit	0	40	...
Seizures	0	9	...
Blood pressure surge	5	46	0.19
Any brain CT or MRI abnormal	4	56	0.61
Subarachnoid hemorrhage	4	43	0.33
Intracerebral hemorrhage	0	15	...
Cerebral infarction	0	13	...
Reversible vasogenic edema	0	12	...
Cervical artery dissection	0	20	...
Persistent deficit at 3 mo	0	12	...
Mean follow-up duration, mo	110±31	110±41	0.97

CT indicates computed tomography; CVD, cardiovascular death; MRI, magnetic resonance imaging; and RCVS, reversible cerebral vasoconstriction syndrome.

Our study has several limitations. It mainly includes patients with typical RCVS with recurrent thunderclap headaches. The follow-up was not done at regular prespecified intervals. The imaging paradigm for recurrent headache was not standardized. Lack of systematic vascular imaging in patients with thunderclap headache might have resulted in an underestimation of the rate of recurrent RCVS. Conversely, observers of the neuroimaging data were not blinded to the clinical status of the patients, which might have induced an overestimation. Because our study did not assess how many patients really avoided vasoconstrictors,

we cannot calculate the relapse rate in avoidant versus non-avoidant patients.

Disclosures

Dr Mawet received travel, accommodation, and meeting expenses from Homeperf, SOS Oxygene, Novartis, and Elsevier, fees from Novartis, outside the submitted work; he is a member of the redaction committee of "La Lettre du Neurologue" without financial compensation. Dr Roos received grants from Novartis and Homeperf, fees from Novartis, Teva, Biogen, and Orkyn, and travel, accommodation, and meeting expenses from Novartis, Teva, and SOS Oxygene, all outside the submitted work. Dr Ducros received honoraria for board membership

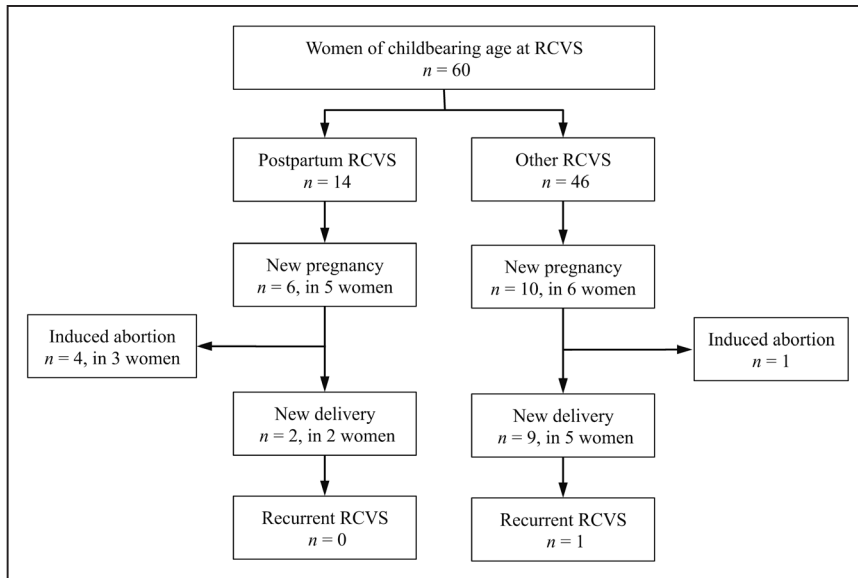


Figure 2. Follow-up of women of childbearing age at initial reversible cerebral vasoconstriction syndrome (RCVS).

from Novartis, Lilly, Teva and Amgen, speaker fees from Novartis, and travel, accommodation, and meeting expenses from Novartis and Teva, all outside the submitted work. The other authors report no conflicts.

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